Modification of Cardiopulmonary and Intestinal Motility Effects of Xylazine with Glycopyrrolate in Horses

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ABSTRACT

Xylazine (XYL) administration in horses is accompanied by significant cardiovascular depression characterized by a 25–35% decrease in cardiac output (CO) which is likely to compromise tissue oxygen delivery (DO_2), and usually vagally mediated bradycardia is an important cause of this reduced cardiovascular performance. To examine the possible benefit of preventing the bradycardiac response, 6 healthy horses were treated with intravenous (IV) saline (SAL) or 2.5 μg/kg glycopyrrolate (GLY) in a blinded, randomized, crossover trial. Fifteen minutes later, 1 mg/kg XYL was administered IV and systolic, diastolic and mean blood pressures (SBP, DBP, and MBP, respectively), central venous pressure (CVP), mean pulmonary artery pressure, heart rate (HR), CO, and arterial and mixed venous blood gases were measured at the following times: baseline, 2, 5, and 10 min post-SAL or GLY; and 2, 5, 10, 15, 30, 45 and 60 min post-XYL. Determination of cardiac index (CI), stroke index (SI), left ventricular work, systemic vascular resistance (SVR), DO_2, oxygen uptake, and oxygen extraction ratio were made at the same time. Gastrointestinal (GI) motility was evaluated by four-quadrant auscultation for 24 h post-XYL. Statistical analysis of continuous variables was carried out using ANOVA for repeated measures and Wilcoxon's rank-sum test for non-parametric data.

In GLY treated horses, HR, SBP, MBP, DBP, CI, DO_2 and mixed venous oxygen tension were significantly higher up to 30 min after XYL ($P \leq 0.02$) while CVP and SI were significantly lower 2 and 5 min post-XYL, respectively. In both groups, GI motility as assessed by auscultation was virtually abolished for an hour, with a non-significant tendency for the decrease in motility to last longer in the GLY/XYL group. None of the treated horses developed abdominal discomfort. No significant difference was observed in the other variables. The study shows that 2.5 μg/kg GLY premedication reduces the cardiovascular depression caused by 1 mg/kg XYL, without adversely affecting GI motility.

RÉSUMÉ

L'utilisation de xylazine (XYL) chez les chevaux produit des effets cardiovasculaires telle une diminutions de 25 à 35 % de l'éjection cardiaque (EC) qui se répercute par une diminution de l'oxygénation tissulaire (OT) et une bradychardie d'origine vaguale. Afin de contrecarrer cet effet cardiaque, du glycopyrrolate (GLY; 2,5 μg/kg) ou de la saline furent administrés chez 6 chevaux dans une étude à l'aveugle et randomisée selon un modèle expérimental en croisé. Quinze minutes suivant l'administration du GLY, 1 mg/kg de XYL fut administré par voie intra-veineuse et on enregistra les pressions systoliques (PSY), diastoliques (PDI) et moyennes (PM), la pression veineuse centrale (PVC), la pression moyenne de l'artère pulmonaire (MAP), la fréquence cardiaque (FC), l'EC et les gaz sanguins artériels et veineux aux temps 0, 2, 5, 10 min suivant l'injection de GLY et 2, 5, 10, 15, 30, 45 et 60 min après l'injection de XYL. Aux mêmes temps, des mesures de l'index cardiaque (IC) de la puissance cardiaque (PC), du travail ventriculaire gauche, de la résistance vasculaire systémique, de l'OT, de la consommation d'O_2 et de son extraction furent prises. La motilité gastrointestinale (MGI) fut évaluée par auscultation pendant 24 h. Une analyse statistique par ANOVA sur mesures continues fut faite et un test de Wilcoxon fut mené sur les données non paramétriques.

Chez les chevaux traités au GLY, les FC, PSY, PM, PDI, IC, OT et la tension veineuse en oxygène étaient significativement plus grandes ($P \leq$ 0,02) jusqu'à 30 min suivant l'injection de XYL tandis que la PVC (2 min) et l'IC (5 min) étaient significativement plus bas. Dans les deux groupes, la MGI était relativement absente pour 1 h et tendait à être diminuée pour une plus longue période chez le groupe GLY. Par contre, aucun cheval ne démontra de malaise abdominal. Les autres paramètres mesurés n'étaient pas significativement différents entre les deux groupes. Cette étude démontre qu'une prémédication au GLY (2,5 μg/kg) réduit les effets dépresseurs que l'administration de 1 mg/kg de XYL produit au niveau cardio-vasculaire tout en n'affectant pas la motilité intestinale.

(Traduit par docteur Pascal Dubreuil)

INTRODUCTION

Xylazine (XYL) , first developed in 1962, is still the most popular α_2 adrenoceptor agonist sedative drug in large animals (1). Xylazine sedation produces important cardiopulmonary

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alterations in the horse (2). Intravenous administration rapidly induces systemic vasoconstriction by directly acting upon peripheral α_1 and α_2 adrenergic receptors and through a central stimulatory effect which augments the peripheral release of adrenergic neurotransmitters (3). The resulting carotid baroreceptor reflex stimulation enhances the vagal parasympathetic activity and, perhaps accompanied by a negative chronotropic effect (2), produces profound bradycardia and second-degree atrioventricular blocks (2°-AVB). These effects, coupled with reduced central sympathetic discharge (4) and perhaps myocardial depression (5), bring about a 25 to 50% fall in cardiac output (CO) with clinical doses (2,6). This fall in CO may last as long as an hour and contributes to the delayed and persistent hypotension observed clinically. In horses, PaO_2 decreases slightly with little change in $PaCO_2$ (2).

A significant fall in CO ultimately affects oxygen delivery (DO_2), which may decrease further if the horse is anesthetized on room air and develops hypoxemia due to ventilation/perfusion mismatch. Additionally, when XYL is used as a preanesthetic, the resulting cardiovascular compromise might be further aggravated when the horse is transferred to an inhalant anesthetic. Attempted correction of low blood pressure and low flow states with drugs like dobutamine may induce arrhythmias or a poor response in some animals (7).

Bradycardia due to vagal stimulation has been recognized as a key factor in the cardiovascular response to XYL; however, the effect of bradycardia on CO and DO_2 has not been well addressed in previous studies. It was discovered very early that pretreatment with atropine would prevent bradycardia and 2°-AVB (8). Nevertheless, the use of anticholinergic blockade did not gain wide acceptance due to the fact that atropine utilization increases the risk of gastrointestinal (GI) stasis with abdominal discomfort, tympany and colic in some cases (9). In addition, atropine produces unwanted fetal effects when administered in pregnant animals, and disorientation from the mydriatic effect of atropine may seriously affect the quality of equine recoveries from general anesthesia (10).

Glycopyrrolate (GLY), an alternative anticholinergic agent, is free of many of the limitations of atropine. Being a quaternary ammonium compound, it does not cross physiological barriers substantially and, therefore, does not produce significant ocular effects or affect the fetus (11). Previous studies, measuring intestinal transit time in ponies, reported GLY to be equal or less inhibiting than atropine on that variable (12). The present study was carried out to determine whether low dose GLY would improve cardiopulmonary function during xylazine sedation, without adversely affecting GI motility.

MATERIALS AND METHODS

ANIMALS AND INSTRUMENTATION

Six adult horses (2 males and 4 females) with a mean age of 8.5 ± 3.2 (SEM) y and weighing 484.3 ± 38.8 kg were used in this study. All the horses were clinically healthy as established by physical examination, history, a normal lead-1 base apex electrocardiogram (ECG), arterial blood gas analysis and a complete blood count. The animals were not subjected to any other drug administration during and 1 mo prior to this study. Before each experiment, the horses were fasted overnight, with free access to water at all times. During each study, the least possible restraint was used and the experiments were carried out in a quiet, traffic free area to minimize external stimulation. The project was approved by the institutional Animal Care Committee and carried out under the experimental guidelines of The Canadian Council on Animal Care.

Catheters and wire loops were inserted using local infiltration analgesia with 2% lidocaine and aseptic precautions. Alligator clamps were connected to subdermally placed stainless steel wire loops to measure heart rate (HR) and rhythm on a 30 sec trace of a base apex ECG. Any P wave not followed by a QRS complex was considered a 2°-AVB. The incidence of 2°-AVB was based on the number of animals (out of 6) showing at least one blocked wave within a 30 s recording interval, while the frequency was expressed as the proportion of blocked waves during this recording.

A 20 gauge, 5 cm long catheter (Insyte-W, Beckton Dickinson Vascular Access, Sandy, Utah, USA) was placed in the facial or transverse facial artery for recording systolic (SBP), mean (MBP) and diastolic (DBP) blood pressures and for collection of arterial blood. Blood pressure and ECG were recorded using a 4-channel electronic system (Model VSM-1, Physio-Control Corp, Redmond, Washington, USA) with the scapulo-humoral joint as the zero reference level for location of the pressure transducers (Model T-36 AD-R, Viggo-Spectramed, Oxnard, California, USA). The blood pressure measurement system was calibrated before and verified after completion of every experiment with a mercury manometer.

Three introducers (Arrow Percutaneous Introducer Sheath Set, Arrow International Inc, Pennsylvania, USA) placed in the jugular vein (2 on one side and 1 on the other side) facilitated the passage and placement of 3 cardiac catheters using characteristic pressure waveform curves. A thermodilution catheter (Swan-ganz, 129 cm, 7 Fr, Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine, California, USA) was placed in the pulmonary artery for measurement of CO as described elsewhere (13), and to record core body temperature. A 130 cm vialon catheter (2.9 mm o.d., Baxter Corporation, Mississauga, Ontario) in the pulmonary artery was used to collect mixed venous blood gas samples and for measuring mean pulmonary artery pressure (MPAP). A similar catheter was positioned in the right atrium for measuring central venous pressure (CVP) and for administering drugs and the thermodilution injectate. Iced 5% dextrose solution (60 mL) (Baxter Corporation) was used as the injectate solution and was injected in less than 6 s taking suitable precautions to ensure that the injectate did not warm before administration. Cardiac output determinations were made with a computerized system (Model COM-2, P-115, Baxter Edwards Critical Care Division) which permitted a visual display of the thermal curve. The mean of three CO determinations made in rapid succession (and agreeing within 10% of each other) were taken as the CO value at each measuring period.

Three mL arterial and mixed venous blood samples were drawn simultaneously at specified intervals in heparinized air-tight glass syringes containing washers to facilitate thorough mixing of the specimen before analysis. A part of each sample was used for hemoglobin (Hb) estimation (Coulter Hematology Analyzer, Coulter Electronics of Canada Ltd, Burlington, Ontario). Blood samples were stored in ice and underwent blood gas and acid base analysis within 30 min (Model ABL-3, Radiometer, Copenhagen, Denmark), along with determination of the hematocrit (PCV) by the microhematocrit method and total protein (TP) levels by the refractometry method. Blood gas and acid base values were corrected to body temperature. Hemoglobin saturation was calculated using an equation for equine blood which corrects for pH, PCO_2 and temperature effects (14).

The GI motility was evaluated by auscultation, using a modification of the method described elsewhere (9). Four abdominal quadrants (upper and lower, left and right side) were evaluated using at least 30 s auscultation (60 s in the case of low frequency) at each of 2 sites per quadrant by 1 person who was unaware of the treatment. Observations were scored subjectively as 4 (long, loud, gurgling sounds audible at both sites in each quadrant with a frequency of at least 2–4/min), or 3 (similar sounds as described above; but audible only once/min at both sites, or more than once but only at one site in the same quadrant), or 2 (low-pitched crepitation like sounds audible at both sites in a quadrant with a frequency of more than once/min) or 1 (low-pitched crepitation audible only once/min at both sites of a quadrant, or more than once but only at one site of a quadrant), or 0 (no auscultable gut sounds at all throughout the quadrant). Thus, the total score from all quadrants at each observation interval could vary from 0 to 16.

EXPERIMENTAL DESIGN

The study was designed as a blinded, randomized, cross-over protocol, with at least 7 d between subsequent experiments in a horse. After instrumentation, the horses were allowed a period of 15 to 30 min for stabilization before recording 2 baseline observations 15 min apart. Subsequently, they received either 10 mL normal saline (SAL) or 2.5 μg/kg of glycopyrrolate (Robinul, Ayerst Laboratories, Montreal, Quebec) diluted to 10 mL with normal saline. Variables were recorded for 15 min before administering 1.0 mg/kg of xylazine (Anased, Lloyd Laboratories, Shenandoah, Iowa, USA) and for 60 min thereafter at the intervals described below. After recording the last observation at 60 min, the catheters were removed, skin sutures were placed at the catheter insertion sites and a pressure bandage was applied. The horse was returned to its stall when sedation wore off and was offered food immediately. Subsequently, the animals were closely examined for appetite, time to passage of 1st feces and possible signs of abdominal discomfort or colic.

The baseline values for all the variables were taken as the mean of 2 observations which were recorded when the horse was stable and quiet, as evidenced by general demeanor and HR and BP observation on the oscilloscope. The lines were flushed and the correct position of the catheters was ascertained from the pressure waveform display before recording every observation. Variables were recorded at each measurement interval in the order of ECG, pressures (SBP, MBP, DBP, MPAP and CVP), blood gases, CO and GI motility.

Vascular pressures and ECG were recorded at baseline; 2, 5, and 10 min after SAL or GLY administration; and 2, 5, 10, 15, 30, 45 and 60 min post-XYL injection. Cardiac output was recorded at all the above mentioned intervals except 2 min after the administration of drugs. Blood samples were obtained at the baseline period (single sample), 10 min after SAL or GLY; and 5, 15, 30 and 60 min after XYL administration. Gastrointestinal sounds were evaluated at baseline, 10 min post-SAL or GLY; and 0.25, 1, 2, 3, 4, 6, 9, 12, 18 and 24 h after XYL injection.

Derived calculations included: cardiac index (CI = CO ÷ BWt) in mL/kg/min; stroke index (SI = CI ÷ HR) in mL/kg/beat; left ventricular work (LVW = CO × MBP × 0.0135) in kg·m/min; systemic vascular resistance (SVR = 79.9 × {MBP − CVP} ÷ CO) in dynes·sec/cm^5; arterial (CaO_2) and mixed venous ($C\bar{v}O_2$) blood oxygen contents (=[{1.39 × Hb × corrected saturation} + {0.0031 × PO_2}] × 10) in mL/L; oxygen delivery (DO_2 = CO × CaO_2) and oxygen uptake ($\dot{V}O_2$ = CO × {CaO_2 − $C\bar{v}O_2$}) in L/min with the oxygen extraction ratio ($\dot{V}O_2/DO_2$) expressed as a percent (15).

STATISTICAL ANALYSIS

The data were analyzed using Statistical Analysis System (SAS Institute Inc, Box 8000, SAS Circle, Cary, North Carolina, USA). All values are reported as mean ± SEM. Baseline values of the test (GLY) and control (SAL) groups were compared with a paired student's *t*-test using a 95% confidence interval. Wilcoxon's rank-sum test was employed to analyze the frequency of 2°-AVB ($P \leq 0.05$) and non-parametric GI motility observations ($P \leq 0.05$). Both pre- and post-XYL values (except baseline observations) were subjected to an independent two-way multifactorial ANOVA for repeated measures ($P \leq 0.05$). Due to great variability in the 60 min observation as the XYL sedative effect wore off, this sampling interval was not included in the statistical analysis. The variables exhibiting significant change were further examined by one-way ANOVA to identify the intervals at which the 2 treatments significantly differed ($P \leq 0.02$). The baseline observations and a single blood gas observation recorded before XYL administration were analyzed with a paired student's *t*-test ($P \leq 0.05$). A Scheffe's test ($P \leq 0.05$) was applied independently to both the groups to contrast the post-XYL observations with the pre-XYL values under the influence of SAL or GLY; baseline values were excluded from this analysis (16).

RESULTS

The hemodynamic, blood gas and acid base changes are shown in Figure 1 and Tables I and II. Baseline measurements were not different prior to SAL or GLY treatment for any variable measured, other than for the PCV value, which was significantly higher ($P \leq 0.05$) in the SAL treated horses

TABLE I. Cardiovascular changes after intravenous saline (SAL) or 2.5 μg/kg glycopyrrolate (GLY) administration, and followed by xylazine (1.0 mg/kg) in horses[a]

		Time (min)										
			SAL/GLY			XYLAZINE						
Variable[b]	Group	Baseline	2	5	10	2	5	10	15	30	45	60
	SAL	1.4	0	0	0	12.8	14.4	11.6	9.7	6.5	5.2	1.9
Freq HB		± 0.0	± 0	± 0	± 0	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0
(%)	GLY[c]	0	7.7[d]	6.3[d]	4.2[d]	0[d]	0[d]	0[d]	0[d]	0[d]	0[d]	0
		± 0	± 0.2	± 0.3	± 0.1	± 0.2	± 0	± 0	± 0	± 0	± 0	± 0
Incidence of 2°-AVB	SAL	1	0	1	1	5	4	4	3	3	3	1
(no. of horses)	GLY	0	2	1	1	0	0	0	0	0	0	0
	SAL	152	151	154	162	149	153	147	145	140	136	135
SBP		± 10	± 11	± 15	± 12	± 9	± 8	± 7	± 9	± 6	± 6	± 6
(mmHg)	GLY[c]	138	146	146	151	222[d]	215[d]	200[d]	182[d]	155	135	125
		± 6	± 8	± 8	± 8	± 26	± 19	± 17	± 15	± 10	± 7	± 8
	SAL[c]	98	95	100	102	112	119	108	110	105	99	92
DBP		± 7	± 8	± 8	± 5	± 4	± 6	± 6	± 4	± 5	± 3	± 6
(mmHg)	GLY[c]	89	97	102	102	155[d]	148[d]	134[d]	127[d]	111	97	80
		± 3	± 5	± 5	± 5	± 9	± 8	± 6	± 6	± 6	± 6	± 5
	SAL[c]	24	24	25	23	30	26	26	25	24	24	25
MPAP		± 2	± 1	± 1	± 1	± 2	± 2	± 1	± 1	± 1	± 1	± 1
(mmHg)	GLY	24	25	24	27	34	26	24	24	25	23	22
		± 1	± 1	± 1	± 2	± 3	± 3	± 3	± 3	± 1	± 1	± 1
	SAL[c]	2.7	3.1	3.2	2.8	11.7	9	6	7.8	6.7	7.1	5.5
CVP		± 1.2	± 1.3	± 1.3	± 1.3	± 0.6	± 2.1	± 2.9	± 0.9	± 1	± 1.7	± 1.3
(cmH_2O)	GLY[c]	2.4	1.2[d]	0[d]	−0.1[d]	6.2[d]	4.2	2.5	2.2	3.7	1.8[d]	1.3
		± 1.1	± 1.4	± 1.4	± 1.1	± 1.9	± 1.9	± 1.7	± 1.6	± 2.6	± 2	± 1
	SAL[c]	29.2	ND	39.9	32.9	ND	19	19.2	20.5	22.1	24.7	28.5
CO		± 1.8		± 2.4	± 3.3		± 1.4	± 1.5	± 1.5	± 1.8	± 2.8	± 1.9
(L/min)	GLY[c]	29.8	ND	35	34.1	ND	27.9[d]	28.6[d]	30.2[d]	28.1[d]	29.9	28.4
		± 1.5		± 3.2	± 1.7		± 1.3	± 0.9	± 1.1	± 2	± 2.3	± 2.1
	SAL[c]	1.6	ND	1.6	1.7	ND	1.4	1.4	1.5	1.5	1.7	1.8
SI		± 0.1		± 0.1	± 0.2		± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1
(mL/kg/beat)	GLY	1.6	ND	1.6	1.5	ND	1.2[d]	1.3	1.5	1.5	1.6	1.5
		± 0.2		± 0.2	± 0.2		± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1
	SAL[c]	47.5	ND	52.7	55.3	ND	32.2	31	32.7	33.6	36.7	40.3
LVW		± 3.6		± 6	± 6.2		± 4	± 4	± 4	± 3.9	± 5.1	± 3.5
(Kg·m/min)	GLY	43.3	ND	55.7	56.1	ND	67.7[d]	62.4[d]	62.1[d]	48.7[d]	44.4	36.8
		± 2.9		± 6.4	± 4.9		± 5.9	± 5.4	± 4.8	± 5.8	± 4.2	± 3

[a] Mean ± SEM ($n = 6$)

[b] Freq HB: frequency of second degree atrioventricular blocks (2°-AVB); Incid 2°-AVB: incidence of 2°-AVB; SBP: systolic blood pressure; DBP: diastolic blood pressure; MPAP: mean pulmonary arterial pressure; CVP: central venous pressure; CO: cardiac output; SI: stroke volume index; LVW: left ventricular work

[c] Significant difference between pre-xylazine (2, 5, 10 min) and post-xylazine (2–45 min) grouped data ($P \leq 0.05$)

[d] Significantly different from corresponding SAL treatment ($P \leq 0.02$)

ND: Not determined

(35 ± 1.6%) as compared to when receiving GLY (31.3 ± 0.9%).

EFFECT OF GLYCOPYRROLATE

Minimal changes were produced by GLY treatment alone during the 10 min period of observation. There was a tendency for HR to be higher with GLY treatment and for GI motility to be lower (Figure 2) but the changes were not significant. Central venous pressure was significantly lower and the frequency of 2°-AVB was higher at 2, 5 and 10 min after GLY administration. There were no other significant differences noted.

EFFECT OF XYLAZINE

When the post-XYL measurements in the SAL group were compared to the pre-XYL sample periods using Scheffe's test, there was a significant ($P \leq 0.05$) decrease in HR, CI, SI and LVW; whereas CVP, MPAP, SVR, and DBP increased. Arterial and venous hemoglobin levels, PaO_2, $P\bar{v}O_2$, $C\bar{v}O_2$ and DO_2 values were lower after XYL, while $\dot{V}O_2/DO_2$ was higher. In the GLY treatment group, XYL produced no changes in HR, CI, SI, LVW, MPAP, pHa, PCV, TP, arterial/venous hemoglobin levels, $P\bar{v}O_2$, CaO_2, $C\bar{v}O_2$, DO_2 or $\dot{V}O_2/DO_2$ when compared to the pre-XYL values. Arterial blood pressures, CVP, $PaCO_2$, and ABE-a values increased. The magnitude of the decrease in CI was in the order of 35% in the SAL group while, in the GLY group, the post-XYL values for CI were close to the baseline level over the 60 min study (Figure 1). Both groups demonstrated a similar rise in SVR (by 55 to 75%) for 30 min after XYL.

DIFFERENCE BETWEEN TREATMENT GROUPS

Following XYL administration, HR, CI, MBP and LVW were higher in the GLY group than in the SAL group from 2 to 30 min, and SBP and DBP were elevated until 15 min ($P \leq 0.02$). Stroke index and CVP were lower in the GLY group at 2 min. The decreased HR in the control group after XYL was marked, with one animal demonstrating a HR of 18 beats/min. Only 1 horse revealed 2°-AVB block at rest. In the SAL group, XYL precipitated a 2°-AVB block in 5 out of 6 horses, which persisted up to 45 min in 3 animals. The frequency of 2°-AVB block was lower in GLY

treated horses up to 45 min after XYL administration. None of the horses receiving GLY showed 2°-AVB block following XYL administration.

When comparing between treatment groups, there was no difference in $\dot{V}O_2$ values at any time period after XYL administration, but $P\bar{v}O_2$ and $C\bar{v}O_2$ and were lower ($P \leq 0.02$) in the SAL group at 5 and 15 min (Table II). Total DO_2 was greater at 5, 15 and 30 min in the GLY group, with significantly lower $\dot{V}O_2/DO_2$ at 5 min post-XYL. There was no difference between the treatment groups for pHa, ABEa, PaO_2, $PaCO_2$, CaO_2, PCV or hemoglobin values at any time period after XYL administration. The TP values tended to be higher in the GLY group, with the difference being significant ($P \leq 0.02$) at 30 min.

GASTROINTESTINAL MOTILITY

The loss of motility as assessed by auscultation, which was only partial following GLY, became profound and near total following XYL administration in both groups (Figure 2). Subsequent return of motility tended to be delayed in the GLY treated horses. Half the baseline intensity of gut sounds were audible at about 2 and 4 h, and near normal sounds were appreciable at 6 and 9 h in SAL and GLY groups, respectively. Statistically, the GI motility score did not differ significantly between 2 treatments. None of the GLY treated horses revealed any loss of appetite or signs of abdominal discomfort during 24 h following the experiments.

TABLE II . Blood gas, acid base, hematocrit and hemoglobin changes after intravenous saline (SAL) or 2.5 μg/kg glycopyrrolate (GLY) administration, and followed by xylazine (1.0 mg/kg) in horses[a]

		Time (min)					
		SAL/GLY		XYLAZINE			
Variable[b]	Group	Baseline	10	5	15	30	60
PaO_2 (mmHg)	SAL[c]	95.4 ± 3.5	92.6 ± 3.6	80.6 ± 3.9	83.2 ± 4.1	86.6 3.7	89.5 2.4
	GLY[c]	94.9 ± 4.8	95 ± 4.4	83.9 ± 1.9	88.6 ± 2.7	91.7 5.8	92 6.4
$PaCO_2$ (mmHg)	SAL	40.2 ± 0.6	39.7 ± 0.7	40.9 ± 2.0	41.5 ± 1.8	42.6 ± 1.0	42 ± 1.4
	GLY[c]	42.2 ± 1.2	40.5 ± 1.7	43.1 ± 1.1	42.8 ± 1.1	43.6 ± 1.4	43.7 ± 1.3
pHa	SAL	7.42 ± 0.01	7.43 ± 0.01	7.43 ± 0.01	7.41 ± 0.01	7.44 ± 0.01	7.45 ± 0.01
	GLY	7.42 ± 0.01	7.42 ± 0.01	7.41 ± 0.01	7.42 ± 0.01	7.43 ± 0.01	7.43 ± 0.01
ABEa (mEq/L)	SAL	1.8 ± 1.0	1.7 ± 1.1	2.1 ± 0.8	1.8 ± 1.1	3.3 ± 0.9	4.4 ± 1.2
	GLY[c]	2.5 ± 0.6	1.4 ± 0.7	2.6 ± 0.5	2.9 ± 0.5	3.8 ± 0.6	4.6 ± 0.7
$P\bar{v}O_2$ (mmHg)	SAL[c]	33.5 ± 1.5	32.4 ± 2.0	23.6 ± 1.4	25.7 ± 0.7	28.2 ± 1.3	28.5 ± 1.2
	GLY	29.3 ± 1.0	29.6 ± 1.3	29.0[d] ± 1.1	31.4[d] ± 0.6	30.6 ± 0.9	28.2 ± 1.4
PCV (%)	SAL[c]	35.0 ± 1.6	33.4 ± 2.7	33.3 ± 2.4	30.7 ± 1.6	28.5 ± 1.3	25.8 ± 0.9
	GLY	31.3[d] ± 0.9	30.7 ± 2.4	30.6 ± 1.6	29.4 ± 1.8	27.2 ± 1.5	25.8 ± 1.5
Total proteins (g/L)	SAL[c]	67.9 ± 1.9	66.4 ± 2.2	67.4 ± 2.0	63.6 ± 1.8	61.7 ± 2.0	62.3 ± 1.9
	GLY	70.0 ± 3.4	69.9 ± 4.1	69.0 ± 3.8	66.8 ± 3.7	67.0[d] ± 4.4	67.8 ± 5.1
CaO_2 (mL/L)	SAL	158 ± 17	162 ± 29	149 ± 24	135 ± 12	133 ± 9	128 ± 8
	GLY	148 ± 8	156 ± 12	140 ± 5	140 ± 4	138 ± 3	126 ± 5
$C\bar{v}O_2$ (mL/L)	SAL[c]	100 ± 11	94 ± 14	59 ± 12	64 ± 8	70 ± 6	70 ± 6
	GLY	85 ± 6	85 ± 9	76[d] ± 9	80[d] ± 10	79 ± 3	68 ± 4
$\dot{V}O_2$ (L/min)	SAL	1.70 ± 0.30	2.42 ± 0.84	1.63 ± 0.14	1.42 ± 0.07	1.30 ± 0.13	1.60 ± 0.07
	GLY	1.88 ± 0.25	2.42 ± 0.21	1.78 ± 0.12	1.90 ± 0.25	1.71 ± 0.18	1.65 ± 0.15

[a] Mean ± SEM ($n = 6$)

[b] PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; pH_a: arterial pH; ABE_a: arterial adjusted base excess; PCV: packed cell volume; $P\bar{v}O_2$: mixed venous oxygen tension; CaO_2: arterial oxygen content; $C\bar{v}O_2$: mixed venous oxygen content; $\dot{V}O_2$: tissue oxygen consumption

[c] Significant difference between pre-xylazine (2, 5, 10 min) and post-xylazine (2–45 min) grouped data ($P \leq 0.05$)

[d] Significantly different from corresponding SAL treatment ($P \leq 0.02$)

DISCUSSION

The results of this study indicate that GLY pretreatment before XYL administration prevented the bradycardia and onset of 2°-AVB, normalized CI, improved DO_2 and reduced oxygen extraction without altering ventilation, $\dot{V}O_2$ or PaO_2, and without significantly increasing LVW from the pre-sedation period in healthy horses. Although a hypertensive response was observed in horses treated with GLY, the increase in SVR was similar to that seen in control animals. The delay in the return of intestinal motility due to GLY administration was 2 to 3 h and no animal developed GI discomfort.

Doses of GLY ranging from 5 to 40 μg/kg have been advocated for treatment of bradycardia in horses (17,18). The present study shows the effectiveness of a relatively small dose (2.5 μg/kg) for preventing XYL-induced bradycardia and 2°-AVB in horses. Higher doses would presumably interfere with GI motility for a longer period of time and cause unwanted tachycardia (19).

One animal showed a 2°-AVB during baseline recording, an observation which is common in horses. Two animals developed 2°-AVB following GLY administration. The somewhat paradoxical development of 2°-AVB after anticholinergic administration has been associated with low blood levels after intramuscular or subcutaneous administration. This effect occurs because there is an increase in the firing rate of the sinoatrial node before there is an effect on conduction at the atrioventricular node (20). Hemodynamic performance was not

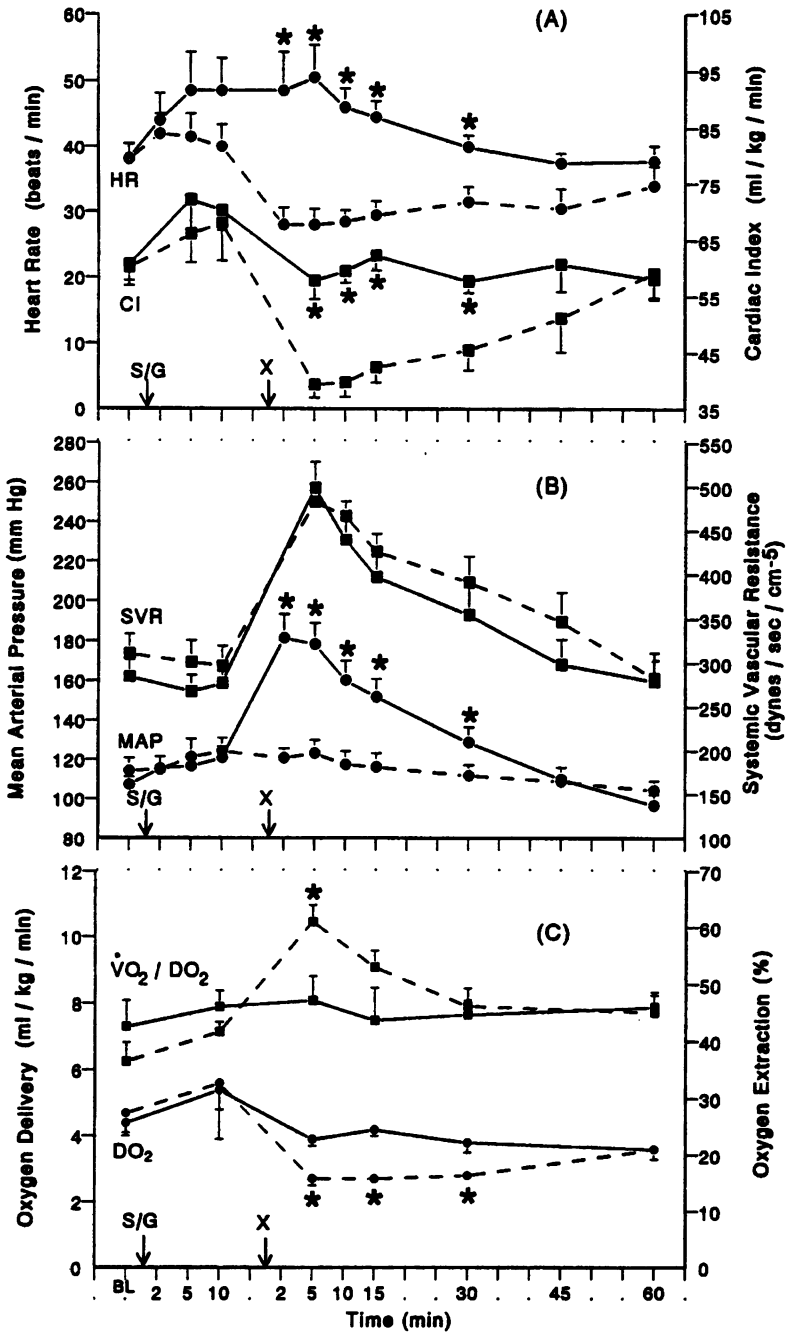

Figure 1. Changes in (A) heart rate and cardiac index; (B) mean arterial pressure and systemic vascular resistance; and (C) oxygen delivery and percent oxygen extraction before (baseline, BL) and after IV saline (- - -) or 2.5 μg/kg glycopyrrolate (___) administration, and followed by xylazine (1.0 mg/kg) in 6 horses. The time of administration of saline (S) or glycopyrrolate (G) and xylazine (X) are shown by arrows. Significant differences ($P \leq 0.02$) between saline and glycopyrrolate treatments are shown (*).

affected adversely at this time as the block was not being accompanied by bradycardia and CI was maintained.

The overall cardiopulmonary response to 2.5 μg/kg GLY per se was minimal, with only a decrease in CVP being observed. While there was a tendency for HR to increase, this change was not significant. Atropine at doses of 0.01 mg/kg and 0.04 mg/kg produced an increase in HR and a decrease in right atrial and ventricular pressures in horses and ponies, without altering BP, CO, CI, LVW and systemic or pulmonary vascular resistance (21,22,23). Anticholinergics reduce right atrial pressure (preload) by causing a decrease in diastolic filling time and possibly by augmenting atrial contractility (20). Although anticholinergics are reported to cause bronchodilation, with an increase in dead space and a fall in PaO_2 (24), the dose of GLY used in the present study did not alter blood gas levels.

Bradycardia, increased afterload and myocardial depression have been implicated as possible causes for a reduction in CO following the administration of α_2 adrenoceptor agonists in horses (2). Although the relative contribution of these factors is unknown, it seems that changes in HR play an important role in reducing CO in XYL treated animals. Klide and coworkers demonstrated a significant correlation between the decrease in HR and a reduction in aortic blood flow in XYL treated dogs (25). Although depression of contractility is reported to be independent of HR (5,26), in the present study CI was sustained near normal values when bradycardia was prevented with prior GLY treatment. The extent of decrease in CI (35%) in control horses, and the overall hemodynamic response, was similar to that reported by others (2,27,28).

The decline observed in PCV, TP and Hb following XYL administration in the present study was similar to that observed in foals (29) and horses (2). It has been ascribed to the accumulation of erythrocytes in the spleen and other vascular reservoirs due to a decrease in sympathetic tone caused by XYL, and to the movement of fluid from the extravascular to the intravascular compartment in response to hyperglycemia (2).

In the present study, salient features of the respiratory and oxygen supply response to SAL/XYL included a significant decrease in PaO_2, $P\bar{v}O_2$ and DO_2 with an increase in oxygen extraction $\dot{V}O_2/DO_2$, in the presence of unaltered $PaCO_2$ or $\dot{V}O_2$. The most commonly observed response of horses and foals to XYL administration has been a substantial decrease in the frequency of breathing without significant alterations in blood gases (8,29). Nevertheless, there are reports of a rise in $PaCO_2$ (30) and a significant fall in PaO_2 following XYL administration in horses (22,31). Numerous factors have been implicated in the fall in PaO_2 when it

occurs after XYL, but understanding of this phenomenon is limited (31,32).

Glycopyrrolate administration maintained a near normal CI in XYL treated horses by increasing HR, and possibly by supporting myocardial contractility. The link between HR, CI and DO_2 is quite evident when the time frames of the changes are examined simultaneously. Xylazine-induced vagal stimulation causes the release of acetylcholine which reduces the development of tension in the contracting myocardium by blocking the release of norepinephrine at adrenergic nerve terminals in the heart, and through a reduction in the stores of cyclic adenosine 3′,5′-monophosphate in the myocardium. Anticholinergics improve contractility by blocking this action of acetylcholine primarily in the atria, but some effect is seen in the ventricles also (20). A rise in HR itself increases myocardial contractility (ascending Bowditch staircase effect) which may contribute towards improving CO (5).

Earlier studies in dogs using atropine (0.04 mg/kg) or GLY (0.01 mg/kg) before XYL showed a significant decrease in CO (33,34), probably because the increase in HR to over 150 beats/min interfered with cardiac filling and oxygenation (20). It may well be that lower doses of anticholinergic treatment are effective in preventing bradycardia caused by α_2 adrenoceptor agonists than are required to treat it. A 0.01 to 0.2 mg/kg dose of atropine has been recommended for the treatment of bradycardia in horses (18), however, Gasthuys and coworkers used a lower dose (0.005 mg/kg) to prevent bradycardia with romifidine (40 to 120 μg/kg) (35). In a previous study, we observed that a 5.0 μg/kg dose of GLY was preferable and more useful than 2.5 and 10 μg/kg doses when the objective was to increase HR in normal and unsedated horses (19). In a pilot study with 2 horses at the beginning of the present investigation, when 5.0 μg/kg GLY was used with 1.0 mg/kg XYL, a strong hypertensive response (SBP approaching 300 mmHg) was observed, coupled with an actual decrease in CI (33%). Ponies premedicated with 0.01 mg/kg atropine maintained a normal CO, except for a transient and small (16%) decrease immediately after XYL (0.6 mg/kg) administration; a significantly greater and persistent decrease in CO (36%) was seen with subsequent administration of detomidine (20 μg/kg) (22). The greater decrease in CO during atropine-detomidine administration could be due to a greater increase in SVR with detomidine, although 0.6 mg/kg of XYL and 20 μg/kg of detomidine are not considered to be equipotent doses (36).

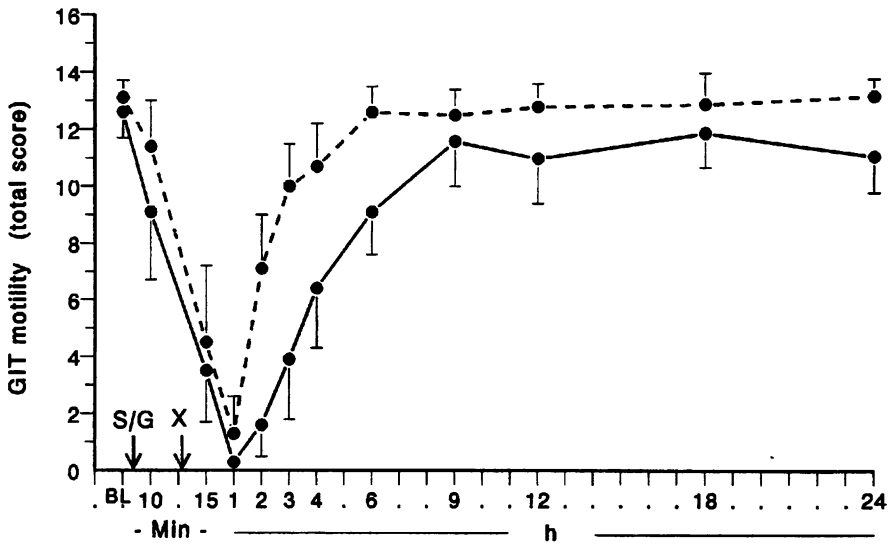

Figure 2. Gastrointestinal (GI) motility before (baseline, BL) and after IV saline (- - -) or 2.5 μg/kg glycopyrrolate (___) administration, and followed by xylazine (1.0 mg/kg) in 6 horses. The time of administration of saline (S) or glycopyrrolate (G) and xylazine (X) are shown by arrows. There was no significant difference between treatments.

Pretreatment with GLY precipitated a hypertensive response. Blood pressure is a function of CO and SVR. In the present study, although SVR increased significantly after XYL administration, the increase was similar in both groups. Thus, the hypertensive response was due to an elevated CI in the GLY group. The magnitude of the hypertensive response in this study was similar to that reported with the use of atropine before XYL in ponies (22) and dogs (25), but less than when atropine was used with detomidine (22) or romifidine in horses (37). The higher BP with detomidine and romifidine could be due to a greater increase in SVR seen with the administration of these drugs, or due to the choice of atropine versus GLY, or the dose employed. The highest mean value of SBP recorded in the present study was 221.5 mmHg. In exercising horses, SBP normally exceeds 200 mmHg by virtue of a 3 to 6 fold increase in CO (38), thus it seems likely that this level of hypertension is safe for at least a short period of time.

No study has actually demonstrated myocardial oxygen balance following the administration of anticholinergics and α_2 adrenoceptor agonists together, however, in unanesthetized ponies coronary perfusion is reported to be maintained even at HR exceeding 200 beats/min and is more affected by hypotension (39). Myocardial oxygen demand is proportional to the work performed. In the present study, LVW decreased with SAL/XYL due to bradycardia, while in GLY treated horses it did not differ significantly between the pre- and post-XYL phase. Similar results have been reported with the use of atropine (0.01 mg/kg) before XYL (0.6 mg/kg) and detomidine (20 μg/kg) in horses (22). Maintenance of normal CI with GLY (as in this study) should maintain myocardial circulation at an adequate level.

Glycopyrrolate pretreatment produced an improvement in DO_2 after sedation with XYL, and prevented the increase in $\dot{V}O_2/DO_2$ observed with SAL/XYL treatment. This is obviously a beneficial effect, albeit one that may not be of great clinical relevance in healthy, conscious horses. Xylazine has been widely utilized for sedation of horses for many years with few serious complications,

irrespective of the bradycardia it produces (1,2,30). Nevertheless, during XYL sedation, the oxygen supply to individual organ(s) may be significantly compromised due to peripheral vasoconstriction. The peripheral vasoconstriction is due to the direct vascular effect of the drug, and to the reflex response of the body produced by bradycardia with a 30 to 50% fall in CO (40). In diseased animals, or when sedation is to be followed by the administration of an anesthetic agent, it may well be beneficial to utilize GLY to maintain CI and DO_2.

Abdominal auscultation is routinely used as a technique to quickly evaluate the status of GI motility in equine health and disease. Although the information gained by this method might not be as definitive as obtained by endoscopy, cinefluoroscopy or intra- and extraluminal pressure measurements, it is non-invasive, practical, clinically useful, and has been used previously to evaluate the effect of drugs on GI function (9). In an earlier study in conscious, unsedated horses an IV dose of 2.5 μg/kg GLY tended to decrease GI motility but the change was not significant (19). A similar response occurred in the present study up to 15 min after GLY administration. With the administration of XYL, GI motility ceased in both SAL/XYL and GLY/XYL treated horses, and the recovery of GI motility tended to be slower in the GLY group.

Xylazine decreases the myoelectric (41) and mechanical (42) activity of the cecum and colon in a dose-dependent manner, similar to the response with atropine but of shorter duration (43). Local blood flow of the bowel decreases by as much as 70% after XYL administration (44), which is substantially more than the corresponding fall in CO. The effect on GI motility is related to α_2 receptor activity, and it is also observed with detomidine sedation (46).

In the present study, the return of GI motility, as assessed by auscultation, was delayed with GLY treatment. Cholinergic parasympathetic mechanisms are integrally involved in the regulation of motor and sphincter functions of the GI tract, and anticholinergics inhibit these activities in a dose-dependent manner for a period which usually outlasts their cardiovascular effects (9,19). In a study comparing the GI effects of atropine and GLY in ponies, normal motility was restored in 2 to 6 h with GLY (5.0 μg/kg), compared to 3 to 12 h with atropine (0.044 mg/kg) (12).

The clinical significance of a 2 to 3 h additional delay in the return of GI motility seen with GLY pretreatment is open to question. None of the horses developed signs of abdominal pain despite the fact that the horses commenced eating within 2 h of GLY/XYL administration. Feces were passed in a number of horses before full return of GI motility as evaluated by auscultation. It would appear, therefore, that low dose GLY pretreatment is safe from the viewpoint of GI function in healthy horses. Further study is needed to clarify the situation when GI motility is already compromised, or with longer acting α_2 adrenoceptor agonists.

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REFERENCES

1. **MAZE M, TRANQUILLI W.** Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. Anesthesiol 1991; 74: 581–605.
2. **WAGNER AE, MUIR WW, HINCHCLIFF KW.** Cardiovascular effects of xylazine and detomidine in horses. Am J Vet Res 1991; 52: 651–657.
3. **SCHMITT H, FOURNADIJEV G, SCHMITT G.** Central and peripheral effects of 2-(2,6-dimethyl phenyl amino)-4-H-5,6-dihydro-1,3-thiazin (Bayer 1470) on the sympathetic system. Eur J Pharmacol 1970; 10: 230–238.
4. **ANTONACCIO MJ, ROBSON RD, KERWIN L.** Evidence for increased vagal tone and enhancement of baroreceptor reflex activity after xylazine (2-(2,6-dimethylphenylamino)-4-H-5,6-dihydro-1,3-thiazine) in anesthetized dogs. Eur J Pharmacol 1973; 23, 311–315.
5. **MUIR WW, PIPER FS.** Effect of xylazine on indices of myocardial contractility in the dog. Am J Vet Res 1977; 38: 931–934.
6. **HUBBELL JAE, BEDNARSKI RM, MUIR WW.** Xylazine and tiletamine-zolazepam anesthesia in horses. Am J Vet Res 1989; 50: 737–742.
7. **DONALDSON LL.** Retrospective assessment of dobutamine therapy for hypotension in anesthetized horses. Vet Surg 1977; 17: 53–57.
8. **KERR DD, JONES EW, HUGGINS K, EDWARDS WC.** Sedative and other effects of xylazine given intravenously to horses. Am J Vet Res 1972; 33: 525–532.
9. **DUCHARME NG, FUBINI SL.** Gastrointestinal complications associated with the use of atropine in horses. J Am Vet Med Assoc 1983; 182: 229–231.
10. **HALL LW, CLARKE KW.** Veterinary Anaesthesia, 9th ed. Philadelphia: Bailliere Tindall, 1991: 73, 214.
11. **MIRAKHUR RK, DUNDEE JW.** Glycopyrrolate: Pharmacology and clinical use. Anaesth 1983; 38: 1195–1204.
12. **ROBERTS MC, ARGENZIO A.** Effects of amitraz, several opiate derivatives and anticholinergic agents on intestinal transit in ponies. Equine Vet J 1986; 18: 256–260.
13. **MUIR WW, SKARDA RT, MILNE DW.** Estimation of cardiac output in the horse by thermodilution technique. Am J Vet Res 1976; 37: 697–700.
14. **ANDERSON LS, SMALE K.** A mathematical model to describe the oxygen-haemogobin equilibrium curve of the thoroughbred horse. J Vet Anaesth 1990; 17: 49.
15. **BOYD CJ, McDONELL WM, VALLIANT A.** Comparative hemodynamic effects of halothane and halothane-acepromazine at equipotent doses in dogs. Can J Vet Res 1990; 55: 107–112.
16. **STEEL RGD, TORRIE JH.** Principles and Procedures of Statistics — A Biomedical Approach. New York: McGraw-Hill Book Co, 1980.
17. **BENSON GJ, THURMON JC.** Intravenous anesthesia. Vet Clin N Am Equine Pract 1990; 6: 513–528.
18. **MUIR WW, HUBBELL JAE**, eds. Equine Anesthesia — Monitoring and Emergency Therapy. St. Louis: Mosby Year Book Inc, 1991: 87, 479.
19. **SINGH S, McDONELL WN, YOUNG S, DYSON DH.** The effect of glycopyrrolate on heart rate and intestinal motility in conscious horses. J Vet Anaesth (in press).
20. **MUIR WW.** Effects of atropine on cardiac rate and rhythm in dogs. J Am Vet Med Assoc 1978; 172: 917–921.
21. **GASTHUYS F, MUYLLE E, MOOR AD, VLIERBERGHE LV, NAGLES L.** Influence of premedication and body position during halothane anaesthesia on intracardial pressures in the horse. J Vet Med A 1988; 35: 729–738.
22. **GASTHUYS F, MOOR AD, PARMENTIER D.** Haemodynamic changes during sedation in ponies. Vet Res Commun 1990; 14: 309–327.
23. **HINCHCLIFF KW, McKEEVER KH, MUIR WW III.** Hemodynamic effects of atropine, dobutamine, nitroprusside, phenylephrine, and propranolol in conscious horses. J Vet Intern Med 1991; 5: 80–86.
24. **DeMOOR A.** Influence of atropine on arterial oxygen tension, acid-base status and tissue hypoxia in the conscious horse. Zbl Vet Med [Reihe A] 1968; 15: 494–498.
25. **KLIDE AM, CALDERWOOD HW, SOMA LR.** Cardiopulmonary effects of

xylazine in dogs. Am J Vet Res 1975; 36: 931–935.
26. **DUNKLE N, MOISE NS, SCARLETT-KRANZ J, SHORT CE.** Cardiac performance in cats after administration of xylazine or xylazine and glycopyrrolate: Echocardiographic evaluations. Am J Vet Res 1986; 47: 2212–2216.
27. **MUIR WW, SKARDA RT, SHEEHAN W.** Hemodynamic and respiratory effects of a xylazine-acetylpromazine drug combination in horses. Am J Vet Res 1979; 40: 1518–1522.
28. **GARNER HE, AMEND JF, ROSBOROUGH JP.** Effect of BAY VA 1470 on cardiovascular parameters in ponies. Vet Med Sm Anim Clin 1971; 66: 1016–1021.
29. **CARTER SW, ROBERTSON SA, STEEL CJ, JOURDENAIS SW.** Cardiopulmonary effects of xylazine sedation in the foal. Equine Vet J 1990; 22: 384–388.
30. **CLARKE KW, HALL LW.** Xylazine — a new sedative for horses and cattle. Vet Rec 1969; 85: 512–517.
31. **LAVOIE JP, PASCOE JR, KURPERSHOEK CJ.** Effects of xylazine on ventilation in horses. Am J Vet Res 1992; 53: 916–920.
32. **LAVOIE JP, PASCOE JR, KURPERSHOEK CJ.** Effect of head and neck position on respiratory mechanics in horses sedated with xylazine. Am J Vet Res 1992; 53: 1652–1657.
33. **KOLATA RJ, RAWLINGS CA.** Cardiopulmonary effects of intravenous xylazine, ketamine, and atropine in the dog. Am J Vet Res 1982; 43: 2196–2198.
34. **GROSS ME, TRANQUILLI WJ, THURMON JC, BENSON GJ, OLSON WA.** Hemodynamic effects of intravenous midazolam-xylazine-butorphanol in dogs. Vet Surg 1990; 19: 173–180.
35. **GASTHUYS F, PARMENTIER D, GOOSSENS L, MOOR AD.** Preliminary study of the efficacy of a low dosage of atropine sulphate on the bradycardia and heart blocks induced by a new α_2 agonistic sedative (Romifidine) in the horse. Proc 4th Intl Cong Vet Anaesth, Utrecht, 1991: 11.
36. **ENGLAND GCW, CLARKE KW, GOOSSENS L.** A comparison of the sedative effects of three α_2-adrenoceptor agonists (romifidine, detomidine and xylazine) in the horse. J Vet Pharmacol Ther 1992; 15: 194–201.
37. **YOUNG LE, LONG KJ, CLUTTON RE, MOLONY V, DARKE PGG.** Influence of atropine sulphate on haemodynamic effects of romifidine hydrochloride in horses. Proc 5th Intl Cong Vet Anesth, 1994: 131.
38. **EVANS DL.** Cardiovascular adaptations to exercise and training. Vet Clin N Am: Equine Pract 1985; 1: 513–531.
39. **PARKS C, MANOHAR M, LUNDEN G.** Regional myocardial blood flow and coronary vascular reserve in unanesthetized ponies during pacing induced ventricular tachycardia. J Surg Res 1983; 35: 119–131.
40. **FOSSE RT, GRONG K, STANGELAND L, LEKVEN J.** Anesthetic interaction in cardiovascular research models: Effects of xylazine and pentobarbital in cats. Am J Vet Res 1987; 48: 211–218.
41. **RUTKOWSKI JA, ROSS MW, CULLEN K.** Effects of xylazine and/or butorphanol or neostigmine on myoelectric activity of the cecum and right ventral colon in female ponies. Am J Vet Res 1989; 50: 1096–1101.
42. **CLARK ES, THOMPSON SA, BECHT JL, MOORE JN.** Effects of xylazine on cecal mechanical activity and cecal blood flow in healthy horses. Am J Vet Res 1988; 49: 720–723.
43. **LOWE JE, SELLERS AF, BRONDUM J.** Equine pelvic flexure impaction. A model used to evaluate motor events and compare drug responses. Cornell Vet 1980; 70, 401–412.
44. **ADAMS SB, LAMAR C, MASTY J.** Motility of distal portion of the jejunum and pelvic flexure in ponies: Effect of six drugs. Am J Vet Res 1984; 45: 795–799.
45. **RUTKOWSKI JA, EADES SC, MOORE JN.** Effects of xylazine butorphanol on cecal arterial blood flow, cecal mechanical activity, and systemic hemodynamics in horses. Am J Vet Res 1991; 52: 1153–1158.
46. **ROGER T, RUCKEBUSCH Y.** Colonic α_2-adrenoceptor-mediated responses in the pony. J Vet Pharmacol Ther 1987; 10: 310–318.